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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,574	11/09/2001	Cesare Peschle	9855-26U3	3808

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/007,574	PESCHLE, CESARE	
	Examin r	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this c mmunication appears n th c ver she t with the c rresp ndence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,32,46,50 and 54* is/are pending in the application.

4a) Of the above claim(s) *12,18,32 50 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-18, 32, 46, 50 and 54 are pending

1. Applicant's election of Group I, claims 1-11, 13-17 and 46 and post natal tissue as specific tissue, epithelial cells as specific type of mammalian cell and cord blood as specific post natal tissue in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Upon further consideration, the prior art search has been extended to include all species of a tissue selected from the group recited in claims 6 and 9 and all species of differentiated mammalian cell as recited in claim 17. The species election is hereby withdrawn.

Claims 12, 18, 32, 50 and 54 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-11, 13-17 and 46 are under consideration in the instant application.

2. The filing date of the instant claims is deemed to be the filing date of the instant applications, i.e. 11/09/2001, as the parent application 09/322,352 does not support the claimed method of generating a differentiated human cell of a selected type, comprising maintaining an isolated human KDR^+ stem cell in the presence of a differentiated mammalian cell of the selected type, the limitations of the instant application. If applicants disagree, applicants should present a detailed analysis as to why the claimed subject matter has clear support in the parent application.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-11, 13-17 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that KDR1 and KDR2 antibody, recited in claim11 are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. A product could be commercially available but only at a price that effectively eliminates accessibility to those desiring to obtain a sample. The relationship between the applicant relying on a biological material and the commercial supplier is one factor that would be considered in determining whether the biological material was known and readily available. However, the mere fact that the biological material is commercially available only through the patent holder or the patent holder's agents or assigns shall not, by itself, justify a finding that the necessary material is not readily available, absent reason to believe that access to the biological material would later be improperly restricted. Moreover, the concepts of "known and readily available to the public" are considered to reflect a level of public accessibility to a necessary component of the invention disclosure that is consistent with the ability to make and use the invention. Neither concept alone is sufficient. A material may be known in the sense that its existence has been published, but is not available to those who wish to obtain that particular known biological material. Likewise, a biological material may be available in the sense that those having possession of it would make it available upon request, but no one has been informed of its existence (See MPEP 2404.01). The applicant did not make of record any of the facts and circumstances surrounding the access to KDR1 and KDR2 antibody at the time the invention was made.

Also an issue is that the Specification does not reasonably provide enablement for a method of generating a differentiated human cell of a selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated any mammalian cell of the selected type as claimed in claims 1-11 and 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type., as claimed in claim 46 wherein the stem cell is separated from the differentiated mammalian cell by *any* porous barrier , as claimed in claim 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses that post natal CD34+KDR+ cells were injected in non-immunocompromised murine blastocytes and the fate of the injected human cells during murine embriogenesis and post-natal life was followed (see Example 4 of the Specification as filed) or injected into the regenerating muscle (see Example 5 of the Specification in particular). Human donor contribution was evaluated by chromosome 17-specific PCR on genome DNA prepared from isolated embryonic and newborn tissue or by RT-PCR using human specific primers for the Myo-D. The Specification disclosed that Cd34+KDR+ cells comprise cell with a capacity to defferentiate into variety of tissue of ecto-meso and endodermic origin (see page 65, lines 5-10 in particular).
It is not clear from the specification how homogeneous is the population of natal CD34+KDR+ primitive stem cell that give rise to both hematopoietic and stromal stem cell population. There is no disclososure on how homologeneous is this cell population (e.g. 90%, 95% or 99%). It is very possible that the cell population contain heterogeneous cell population that give rise to both hemopoietic and stromal elements. What was the sensitivity of the method for selecting natal CD34+KDR+ primitive stem cell, what is the accurate and reproducible quantification of such selection. One skilled in the art would not know the homogeneous nature of the natal CD34+KDR+ primitive stem cell using the teaching of the specification alone. Moreover, Waoller et al. (Blood, 1995, v.85, pages 2422-2435) teach that there is no solid evidence for a hypothesis of a "common stem cell" (see page 2422 in particular). Based on the analysis of over 30,000 stem cells with a variety of CD34+ phenotypes and 864 stromal culture , Waoller et al. concluded that the is no evidence that a single cell can differentiate along both a hematopoietic and stromal lineage (see page 2434 in particular). In addition, Holden et al. (Science, 2002, V.296, pages 2126-2129) teach that thre is no evidence that purified blood stem cells can contribute to any other tissue (see page 2127 in particular).
It is also not clear from the Specification how it was asserted that the injected human donor post natal CD34+KDR+ cells differentiated into any specific cell type as claimed in claim 17. There is no characterization of these cells as to phenotype or functional capacity. It is possible that these cells are an irrelevant contamination of the stem cells selection process or do not provide function associated with stromal microenvironment. Moreover, there is no evidence from the Specification that there was no fusion of the CD34+KDR+ cells with cells of the other lineages. Holden et al. (Science, 2002, V.296, pages 2126-2129) teach that cells can mutate and develop markers characteristics of other lineages or that cells injected into a foreign tissue can take up local DNA and thus appears to have changes identity (see page 2126 in particular). Moreover, Holden et al. further teach that fusion scare has given further impetus to effort to establish

rigorous standards for demonstrating plasticity such as: the cells must be properly identified at the outset, because a single alien cellin ostensibly purified culture could produce misleading results. The cells must contribute to the function of the host tissue. There is no indication that demonstrate functionality of said cells in the specification.

Also the issue is that the specification does not teach how to extrapolate data obtained from *in vivo* studies wherein post natal CD34+KDR+ cells were injected in non-immunocompromised murine blastocytes or injected into the regenerating mirine muscle to the development of effective *in vivo or in vitro* methods of generating a differentiated human cell of a specific selected type, such as the recited in claim17, wherein isolated human KDR+ stem cells are maintained in the presence of any differentiated mammalian cell or in a medium conditioned to reflect the presence of any differentiated mammalian cells, whereby the stem cell differentiated to become the differentiated human cell of the selected type, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a methods of generating a differentiated human cell of a specific selected type, such as recited in claim17, wherein isolated human KDR+ stem cells are maintained in the presence of any differentiated mammalian cell or in a medium conditioned to reflect the presence of any differentiated mammalian cells, whereby the stem cell differentiated to become the differentiated human cell of the selected type.

Thus the specification fails to demonstrate that isolated human KDR+ stem cells can be generated to differentiate into any differentiated human cell by maintaining an isolated human KDR+ stem cell in the presence of a differentiated mammalian cell of the selected type as claimed in claims 1-11 and 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type, as claimed in claim 46 and the art does not recognize that a single cell can differentiate along both a hematopoietic and stromal lineage. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).

Also, the issue is that the specification does not reasonably provide enablement for a method of generating a differentiated human cell of a selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated mammalian cell of the selected type, wherein the stem cell is separated from the differentiated mammalian cell by *any* porous barrier , as claimed in claim 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Specification at page 14, lines 5-10 indicates that an important aspect of the invention is that KDR^+ stem cells can be induced to differentiate into a selected cell type by maintaining said cells in the presence of cytokines and other small molecules secreted by differentiated cells. Stated differently, it is essential for the invention that cytokines and other small molecules can

pass through porous barrier. Applicant himself acknowledge that not *any* porous barrier but only specific porous barrier through which a small proteins (MW< 50,000) can pass, but through which cell cannot pass can be used (see page 14, lines 25-30 of the Specification as filed).

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of generating a differentiated human cell of a selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated any mammalian cell of the selected type as claimed in claims 1-11 and 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type, as claimed in claim 46 wherein the stem cell is separated from the differentiated mammalian cell by *any* porous barrier , as claimed in claim 4. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 1-9, 13-17 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of a method of generating a differentiated human cell of a selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated any mammalian cell of the selected type as claimed in claims 1-11 and 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type., as claimed in claim 46 wherein the stem cell is separated from the differentiated mammalian cell by *any* porous barrier , as claimed in claim 4and wherein the stem cell is isolated from a human hematopoietic tissue using any reagent that specifically binds with KDR.

The specification fails to describe any reagent other then antibody, that specifically binds with KDR. Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of reagent that specifically binds with KDR may be achieved by means of a recitation of a representative number of reagents falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-3, 5-10, 13-17 and 46 rejected under 35 U.S.C. 103(a) as being unpatentable over Bruder et al (US Paten NO:5,736396) in view of Lemischka (US Patent 5,912133) and as evidenced by the Specification disclosure on page 63, lines 4-8 and page 4, lines 4-10.

US Patent '396 teaches a method of generating a differentiated cell of a selected type by incubation human mesenchymal stem cells in the presence of differentiated mammalian cells or condition medium that are effective to induce differentiation into a lineage of choice.(see entire document, Abstract , Column 1, lines 50-55 and Fig.1 in particular). US Patent '396 teaches that human mesenchymal stem cells can be isolated from various tissues that contained stem cells (see column 4 , lines 10-65 in particular). US Patent '396 teaches that human mesenchymal stem cells can be either injected at the site of skeletal defects or incubated in the presence of differentiated cells (see column 5, lines 11-20 in particular).

US Patent '396 does not teach that stem cells are human KDR^+ stem cells.

US Patent '133 teaches a method of isolating human FLK^+ stem cells using antibody that specifically binds FLK-1 (see entire document, Abstract in particular). The Specification on page 63, lines 4-8 disclosed that human KDR^+ stem cells are the same subpopulation of $CD34^+$ of cells as human FLK^+ stem cells. US Patent '133 teaches that human FLK^+ stem cells can be obtained from various tissues that contained stem cells (see column 14, lines 20-50). US Patent '133 teaches that isolated human FLK^+ stem cells have an ability to differentiate *in vitro* or *in vivo*. This ability has an important therapeutic applications (see overlapping column 7 and 8 in particular) .

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '133 to those of US Patent '396 and substitute isolated human mesenchymal stem cells to isolating human KDR^+ stem cells to obtain a claimed method of generating a differentiated human cell of a selected type comprising maintaining an isolated KDR+ stem cells in the presence of a differentiated mammalian cells of the selected type.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because isolated human KDR^+ stem cells can be induced to differentiate *in vitro* or *in vivo* and this ability has an important therapeutic applications as taught by US Patent '133 . This subpopulation of human stem cells can be used to generated a differentiated human cell of a selected type by the method taught by US Patent '396 .

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 6-9 are included because it would be conventional and within the skill of the art to identify various tissues that contained KDR^+ stem cells. Moreover, Applicant himself acknowledge that any tissue that contains stem cells can be used (see page 4, line 4-10 of the instant Specification in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges or conditions

involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Claims 14-16 are included because it would be obvious , conventional and within the skill of the art to use differentiated mammalian cells of different origin, since US Patent '396 teaches a method of generating a differentiated cell of into a lineage of choice. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges or conditions involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

11. No claim is allowed.

12. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
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August 25, 2003

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